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Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington. D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
(302) 774-6443

4/26/93

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation 's TSCA §8(e) reporting standard[2]. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.[3] Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

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[2]In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not.exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent[4], the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- othe "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.[5];

- othe "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- othe "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

[5] *See, e.g.* 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

> Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). *See also*, Rollins Environemntal Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

> ...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

> "a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See,* 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy",43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	}[6]	}[7]
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y[8]
SKIN SENSITIZATION (ANIMALS)	N	Y[9]
EYE IRRITATION	N	Y[10]
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y[11]
REPRODUCTION STUDY	N	Y[12]
DEVELOPMENTAL TOX	Y[13]	Y[14]

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[6] 43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL unknown effects occurring during such a range test may have to be reported if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

[7] Guide at pp.22, 29-31.

[8] Guide at pp-34-36.

[9] Guide at pp-34-36.

[10] Guide at pp-34-36.

[11] Guide at pp-22; 36-37.

[12] Guide at pp-22

[13] 43 Fed Reg at 11112

"Birth Defects" listed.

[14] Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y}[20]	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS #110-89-4
Chem: Piperidine
Title: Toxicity of compounds used in hydrogen reduction building
Date: 5/9/49
Summary of Effects: Paralysis of the CNS and skeletal muscle nerve endings

MR-187
Report # 13-19

cc: A.C. Stevenson - Jackson Laboratory
C.H. Gehrmann, M.D. - Medical Div.
" F. Fuller, Louisiana, 6-7-49

May 9, 1949

DR. E. E. EVANS
MEDICAL DIVISION
CHAMBERS WORKS

TOXICITY OF COMPOUNDS USED IN HYDROGEN REDUCTION BUILDING

Preliminary oral toxicity studies have been carried out under Medical Research Project MR-187 on a series of compounds used in the Hydrogen Reduction Building No. 750. The eleven compounds tested were Orthoanisidine, n-Butyl-p-aminophenol, 2-Chlor-amino-toluene, p-Toluidine, p-Nitroaniline, p-Nitrodichlorobenzene, p-Nitrophenetole, Alpha naphthol, Naphthionic acid, Piperidine, & Diagen A.

Acute oral toxicity was tested by determining the approximate lethal dose (ALD) for rats. The method of Deichmann and LeBlanc* was used wherein single doses of increasing amounts were given to a series of rats by stomach tube. The minimum dose which killed was considered the ALD.

Chronic or cumulative toxicity was tested by administering orally to 6 rats approximately 1/5 the ALD five times a week for 2 weeks so that a total of twice the lethal dose was administered. The rats were checked for change in weight and any unusual clinical symptoms. Following the final treatment they were observed for a period of from one to two weeks prior to being sacrificed. Tissues of all rats were examined for gross and micropathology.

The details of the tests performed for each compound were as follows:

o-Anisidine

Acute Oral Toxicity: The ALD for rats was found to be 1500 mg/kg. The material was administered by stomach tube as a 50% solution in peanut oil. The rat receiving the 1500 mg/kg dose died within 48 hours after treatment. The lungs were found to be congested and edematous.

*Wm. Deichmann and T. J. LeBlanc, J. Ind. Hyg. & Tox.: 25, 415, 1943.

Chronic Oral Toxicity: Ten doses of 300 mg/kg as a 10% solution in peanut oil were administered to 6 rats over a period of two weeks. The rats showed an initial loss of weight but a subsequent normal gain. When sacrificed, no pathology was found which could be attributed to o-anisidine.

Conclusions: From the standpoint of oral toxicity, o-anisidine is not a very toxic compound. 1500 mg/kg were required to produce death in the rat. In addition, cumulative toxicity did not occur under the conditions described.

n-Butyl-p-aminophenol

Acute Oral Toxicity: The ALD was found to be 450 mg/kg. The compound was administered as a 40% solution in peanut oil heated to 50° C. The animals died within 21 hours. The only pathology noted was the presence of albumin in the kidneys.

Chronic Oral Toxicity: Ten treatments of 90 mg/kg each as a 5% solution in peanut oil containing 10% acetone were given. The rats were uncomfortable following the treatments. They also showed a definite slowing of the rate of gain in weight until a week after the final treatment, although they did not go below the original weight at any time. They were killed two weeks after the final treatment and no pathology attributable to the material was detected.

Conclusions: n-Butyl-p-aminophenol is a moderately toxic compound when absorbed through the gastro-intestinal tract. There was no evidence of cumulative toxicity under the conditions of our experiment.

Information on the toxicity of this compound in particular has not been reported but the aminophenols in general are known to cause skin sensitization among workers in the dye and photographic industries and to cause the formation of methemoglobin.

2-Chlor-4-Aminotoluene

Acute Oral Toxicity: The material was given as a 50% solution in peanut oil. 1500 mg/kg was found to be the ALD. Pain and weakness occurred 10 minutes after the dose was given and was followed by unconsciousness and

death within 22 hours. Both rats showed slight congestion of the lungs, and one had evidence of gastritis, but the cause of death was not apparent.

Chronic Oral Toxicity: 300 mg/kg as a 10% solution in peanut oil was fed ten times to each of 6 rats. After the third and fourth treatments the rats were ill and cyanotic. The reactions continued after the subsequent treatments but the intensity slackened and by the tenth they showed some improvement. They were killed 11 days after the final dose. Gross and micropathological examination revealed no pathology which could be attributed to 2-Chlor-4-aminotoluene, but foci of blood formation were consistently found in the spleen.

Conclusions: 2-Chlor-4-aminotoluene is not highly toxic as far as single oral doses are concerned. Since other chloranilidines have been shown to cause cyanosis and depression, presumably through formation of methemoglobin, it is probable that the same mechanism is involved with 2-Chlor-4-aminotoluene. This would be consistent with the observations on the chronic treatments in which the decrease in cyanosis during the latter part of the treatment period was probably due to compensatory activity of the hemopoietic system, since foci of blood formation were found in the spleens of the rats.

p-Toluidine

Acute Oral Toxicity: The material was administered as a 50% solution in peanut oil containing 15% acetone. The AID was 1000 mg/kg. The material caused pain, weakness, cyanosis, and death within 44 hours. Pathologic examination indicated damage to the liver and kidneys.

Chronic Oral Toxicity: Ten doses of 200 mg/kg each were given as a 6% solution in peanut oil containing 15% acetone. The rats became pale and weak after six treatments but regained normal strength and color a week after treatment ended. The rats showed a marked loss of weight until the fifth treatment followed by a slow gain until the last week of observation when they began to gain rapidly. They were sacrificed 12 days after the final treatment and showed evidence of damage to the spleen, kidneys and liver.

Conclusions: p-Toluidine is only moderately toxic by single acute oral dose. Its action is apparently similar to that of aniline, causing anemia and formation of methemoglobin. Cases of industrial poisoning from toluidine have been reported and acute cases are usually characterized by

cyanosis and mental confusion which may be due to cerebral anoxia. Injury to the kidneys has been reported in workers, and was also observed in our rats.

p-Nitroaniline

Acute Oral Toxicity: The ALD was determined by administering the compound as a 40% solution in peanut oil and it was found to be 3375 mg/kg. Even sublethal doses caused weakening and cyanosis while lethal doses produced tremors in addition. The urine contained a bright yellow pigment. Microscopic examination indicated damage to the liver, and the kidneys were distended with albuminous fluid.

Chronic Oral Toxicity: p-Nitroaniline in 10 doses of 675 mg/kg each, was administered to rats as a 20% solution in peanut oil. One rat died after the second treatment and one after the sixth. The other four survived the ten doses and were sacrificed after a ten-day observation period. The rats were in pain after each treatment. Their eyes and skin appeared yellow as did the urine, and there was generalized weakness. The average weight of the four survivors showed a sharp drop until the eighth treatment which was followed by a slow rise until the last week of observation which was marked by a rapid gain in weight. The original weight, however, was never again attained.

On microscopic examination the kidneys were observed to have granulation of the tubular epithelium and occasional vacuolation.

Conclusion: The acute oral toxicity of p-Nitroaniline was fairly low, but the results do show a tendency toward cumulative effects, and p-Nitroaniline has frequently been implicated in human cases of poisoning. Lewin (Gifte u. Vergiftungen, 1929) states that 40 mg/kg of p-Nitroaniline by intravenous injection kills animals, and he reports a fatal case of human p-Nitroaniline poisoning of industrial origin. The Encyclopedia of Occupation and Health (International Labor Office) states that the fatal dose for dogs of o-Nitroaniline is 300 mg/kg, and "is certainly smaller for p-Nitroaniline". The route of administration was not described. It is further stated that p-Nitroaniline in practice causes the greatest number of poisoning cases, of dermatitis, and of conjunctivitis.

Lobo-Mendonca, (Indian Med. Gaz. 77, 673) has reported cases of poisoning in textile workers. The dye was absorbed through the skin and caused paralysis of the central nervous system, marked cyanosis and sometimes death. Methemoglobin was found in the blood and hemoglobin and hematoporphyrin were found in the urine.

These results suggest that some species, including human beings, may be relatively more susceptible to p-Nitroaniline than the rat.

p-Nitrochlorobenzene

Acute Oral Toxicity: The material was administered as a 20% solution in peanut oil warmed to 50° C. The ALD was 670 mg/kg. All treated rats became cyanotic. In rats treated with sublethal doses it lasted 24 hours after treatment. The rat receiving 670 mg/kg lived nearly 48 hours after dosing. Pathological examination revealed necrosis and hemorrhage of the liver and incipient necrosis of the convoluted tubules of the kidneys. The bladder contained blood tinged urine.

Chronic Oral Toxicity: Ten chronic doses of 135 mg/kg each as a 5% solution in peanut oil were administered to each of six rats. One rat died after the fourth exposure and one after the eighth. Both these rats were found to have acute necrosis around the hepatic veins of the liver and presence of albumin and casts in the kidney tubules and granular epithelium in the case of one rat. The remaining four rats survived 10 treatments and were sacrificed twelve days after the final treatment. The rats were cyanotic during the early part of the treatment period and showed a rapid loss in weight throughout treatment and a subsequent gain during the observation period. However they barely exceeded their initial weight. The spleens of these animals were large and congested and showed signs of increased blood formation. This increased activity was probably due to the presence of methemoglobin. The nuclei of the liver cells showed slight variation in staining quality and the kidneys evidence of damage.

Conclusions: As in aniline poisoning the nitro benzene compounds produce breakdown products which cause the formation of methemoglobin with subsequent hemolysis and anemia. As far as acute toxicity is concerned p-Nitrochlorobenzene is moderately toxic with an ALD for rats at 670 mg/kg. Regeneration of blood after acute poisoning is fairly rapid.

Chronic exposure to the compound caused similar blood changes and was fatal in the case of two rats. Blood regeneration is slow in chronic exposure and apparently varies greatly with the individual.

p-Nitrophenetole

Acute Oral Toxicity: p-Nitrophenetole was administered as a 25% solution in peanut oil containing 15% acetone and the ALD was found to be 7500 mg/kg. Doses up to 4000 mg/kg produced no symptoms whatsoever. The rat receiving 5000 mg/kg, however, suffered from pain, weakness, and bronchial irritation, for 24 hours after treatment. At the 7500 mg/kg level the rat immediately became ill, unconscious and died within 24 hours. Autopsy disclosed congestion and edema of the lungs.

Chronic Oral Toxicity: Ten doses of 1500 mg/kg each, as a 25% solution in peanut oil-acetone were administered to six rats. They exhibited a slowing in the rate of gain of weight up to the seventh treatment after which there was a normal gain. At no time, however, did they fall below their pre-exposure weight. Three of the rats voided bright yellow urine throughout the treatment period. The animals were killed twelve days after treatment and no pathology was detected.

Conclusions: p-Nitrophenetole is a relatively non-toxic compound, nor did a cumulative toxicity show up under the conditions of our test.

Alpha Naphthol

Acute Oral Toxicity: The ALD was found to be 1000 mg/kg. The material was administered as a 50% solution in peanut oil. Rats receiving lethal doses suffered from diarrhea and died within 18 hours after treatment. Pathological examination indicated congestion and edema of the lungs, albumin in the kidney tubules and superficial necrosis of the stomach.

Chronic Oral Toxicity: Alpha naphthol as a 10% solution in peanut oil was fed ten times in doses of 200 mg/kg. The rats were pale during the treatment period and voided an abnormally large amount of urine. They showed a marked drop in weight throughout treatment but a normal gain during the observation period. Pathological examination indicated no pertinent pathology.

Conclusions: Alpha naphthol was not found to be a highly toxic compound although it is said to be more toxic than Beta naphthol.

The frequency of urination in the rats on chronic exposure was probably due to the known irritating effect of Alpha naphthol on the kidneys. The intensity and duration of our chronic exposure, however, did not produce a degree of organic kidney damage that could be detected grossly or microscopically when the rats were sacrificed 10 days after the last treatment.

Naphthionic Acid

Acute Oral Toxicity: Doses up to 7500 mg/kg as a 50% solution in peanut oil were given to rats. The animals showed no ill effects and all survived. They were sacrificed and gross and microscopic examination of the tissues did not reveal any pathology.

Chronic Oral Toxicity: 2500 mg/kg was fed 10 times to each of 6 rats. They were somewhat uncomfortable after treatment and drank much water. They lost weight until the fifth treatment, gained slowly until the tenth, and gained rapidly during the observation period which lasted 10 days before the rats were sacrificed. No pathology which could be attributed to the compound was detected.

Conclusions: Naphthionic acid is relatively non-toxic when taken under the conditions described.

Piperidine

Acute Oral Toxicity: The ALD was determined to be [illegible] mg/kg when administered to rats as a 50% solution in water. The rats exhibited marked weakness and lethargy and died in from one to ninety hours depending on the size of the dose. Postmortem examination revealed edema of the lungs and necrosis of the stomach.

Chronic Oral Toxicity: 90 mg/kg as a 5% solution in water was given to rats ten times over a two week period. There was a marked loss in weight until the third treatment, followed by a rise to the original weight by the sixth day after the final treatment. Pathological examination indicated necrosis of the liver and possible kidney changes. The remainder of the rats were killed ten days after the final treatment. Four of the five showed possible kidney damage or the presence of hyaline casts.

Conclusions: Piperidine is said to be similar to coniine which is known to cause pronounced paralysis of the central nervous system and of skeletal muscle nerve endings. It is a moderately toxic compound with its ALD of 450 mg/kg and in this dosage takes a relatively long time to kill.

Chronic exposure to piperidine caused a temporary loss in weight and was the probable cause of death of one rat. Kidney damage though slight, appeared in five of the six rats indicating that cumulative toxicity may occur.

Diagen A

Acute Oral Toxicity: Diagen A was administered to rats by stomach tube in its original form. 7500 mg/kg the maximum feasible dose did not kill. The rat receiving this dose, however, when sacrificed 10 days after treatment showed evidence of chronic gastritis localized at junction of squamous and glandular portions.

Chronic Oral Toxicity: Ten doses of 1100 mg/kg each were given to each of 6 rats over a period of two weeks. There was an initial loss of weight but it was followed by a rapid gain. The animals were sacrificed eleven days after the final treatment and no pathology attributable to Diagen A could be detected.

Conclusions: From the standpoint of oral intake Diagen A is relatively non-toxic. Diagen Bordeau which was tested by this laboratory was also found to be equally non-toxic by mouth, but was found to be a mild skin irritant.

General Summary:

The results of our tests are summarized in the following table, in which the compounds are arranged in order of decreasing acute toxicity.

Compound	ALD	Cumulative Effects
Piperidine	450 mg/kg	Yes
n-Butyl-p-aminophenol	450	None observed
p-Nitro-dichlorobenzene	670	Yes
Alpha naphthol	1000	Yes
p-Toluidine	1000	Yes
O-Anisidine	1500	None observed
2-Chlor-4-aminetoluene	1500	Yes
p-Nitroaniline	3375	Yes
p-Nitrophenetole	7500	None observed
Diagen A	7500	None observed
Naphthionic Acid	7500	None observed

While none of these materials is highly toxic, all but the last three are probably toxic enough to cause industrial poisoning in workers. Since most of the compounds tested are either aromatic nitro or amino compounds they have certain toxicological properties in common. One of the first symptoms of poisoning to appear is that of cyanosis. This is primarily due to the formation of methemoglobin and results in a reduction of oxygen capacity which in turn affects those tissues first whose oxygen need is high and especially the central nervous system. Oxidation of these compounds often leads to the production of chemicals which are injurious to the kidneys.

The compounds discussed reach the human organism by skin absorption, by inhalation and by oral ingestion. The first two are the more important industrially. The tests performed give the approximate lethal dose and some idea of the danger of cumulative toxicity. They do not exclude the possibility of pathology occurring when exposure covers very long periods of time.

HASKELL LABORATORY OF
INDUSTRIAL TOXICOLOGY

John H. Foulger, M. D.
Director

BY: John A. Zapp, Jr., Ph.D.
Assistant Director

JAZ:cwf

Triage of 8(e) Submissions

Date sent to triage: _____ NON-CAP (CAP)

Submission number: 12040 A TSCA Inventory: (Y) N D

Study type (circle appropriate):

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Group 2 - Ernie Falke (1 copy total)

(ATOX) SBTOX SEN (w/NEUR)

Group 3 - Elizabeth Margosches (1 copy each)

STOX	(CTOX)	EPI	RTOX	GTOX
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TYPE: (INT) SUPP FLWP

SUBMITTER NAME: E.I. Dupont de Nemours & Company

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 04/25/95

CHEMICAL NAME: SEE ATTACHED

CAS# 110-89-4

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

	INFORMATION TYPE:	P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
(0209)	NEURO (ANIMAL)	01 (02) 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	01 (02) 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
(0215)	CHRONIC TOX (ANIMAL)	01 (02) 04

	INFORMATION TYPE:	P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

	INFORMATION TYPE:	P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:

NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN: C TOX	USE:	PRODUCTION:
(YES)	YES (DROP/REFER)	RAT	LOW		
NO	NO (CONTINUE)		MED — L		
IN TERMIN	REFER		HIGH M → (acute) (H-M)		

CAS SR

* acutely toxic * 1949 Studies (acute) (The recent studies of longer duration are available)

COMMENTS: Most aromatic nitro or amino compounds (11) were tested for ALD, approximate lethal dose in rats. Piperidine and n-butyl-p-aminophenol had ALD [illegible] mg/kg, p-nitroaniline [illegible] benzene 670 mg/kg. Beta naphthol and p-toluidine had 1000 mg/kg, o-anisidine and 2-chloro-4-aminotoluene 1500 mg/kg, N-Nitrosoaniline (3375 mg/kg) and for p-nitrophenetole, naphthionic acid at 7500 mg/kg. The main effect is cyanosis as a result of formation of methemoglobin. Mostly these chemicals are medium to low concern.

```
=> S P-NITRODICHLOROBENZENE/CN
L17             0 P-NITRODICHLOROBENZENE/CN

=> S NAPHTHIONIC ACID/CN
L18             1 NAPHTHIONIC ACID/CN

=> D HIT

L18  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1995 ACS
OTHER NAMES:
CN      ***Naphthionic acid***

=> D HIT RN

L18  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1995 ACS
OTHER NAMES:
CN      ***Naphthionic acid***
RN    84-86-6  REGISTRY

=> S N-BUTYL
=> D HIT CN

L18  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1995 ACS
OTHER NAMES:
CN      ***Naphthionic acid***
CN    1-Naphthalenesulfonic acid, 4-amino- (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN    .alpha.-Naphthylamine-4-sulfonic acid
CN    1,4-Naphthionic acid
CN    1-Amino-4-naphthalenesulfonic acid
CN    1-Amino-4-sulfonaphthalene
CN    1-Naphthylamine-4-sulfonic acid
CN    4-Amino-1-naphthalenesulfonic acid
CN    4-Amino-1-naphthalenesulphonic acid
CN      ***Naphthionic acid***
CN    Piria's acid

=> S N-BUTYL-P-AMINOPHENOL/CN
L19             1 N-BUTYL-P-AMINOPHENOL/CN

=> D HIT CN

L19  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1995 ACS
OTHER NAMES:
CN      ***N-Butyl-p-aminophenol***
CN    Phenol, 4-(butylamino)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN    Phenol, p-(butylamino)- (6CI, 7CI, 8CI)
OTHER NAMES:
CN    Du Pont Gasoline Antioxidant No. 5
CN      ***N-Butyl-p-aminophenol***
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12040

8EHQ - 1092 - 12040

O-Anisidine		90-04-0
[redacted]	N-butyl-p-aminophenol	unknown 103-62-8
[redacted]	2-chloro-4-aminotoluene	95-74-9
p-Toluidine		106-49-0
p-Nitroaniline		100-01-6
p-Nitrodichlorobenzene		89-61-2
p-Nitrophenetole		100-29-8
Alpha naphthol		90-15-3
Naphthionic acid		unknown 84-86-6
Diagen A		unknown

CECATS\TRIAGE TRACKING DBASE ENTRY

CECATS DATA:
Submission # 8EHQ-1092-12040 SEQ A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: E.I. Dupont de Nemours + Company

INFORMATION REQUESTED FLWP DATE:
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0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APPLIUSE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 01/25/95

CHEMICAL NAME:

SEE ATTACHED

CAS#
110-89-4

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0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	

TRIAGE DATE: NON-CBI INVENTORY
(YES)
CAS SR NO

ONCO/IMMO REVIEW
YES (DROP/REFER)
NO (CONTINUE)

SPECIES
RAT

TOXICOLOGICAL CONCERN:
(LOW) all other chemicals
(MED) pipendine
HIGH

USE: PRODUCTION:

12040A

L

o-Anisidine: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥1,500 mg/kg. The lungs of the 1,500-mg/kg rat were congested and edematous.

M

n-Butyl-p-aminophenol: Acute oral toxicity in rats is of moderate concern. Single oral gavage doses to rats (1/dose) were lethal at ≥450 mg/kg. Albumin was present in the kidneys.

L

2-Chlor-4-aminotoluene: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥1,500 mg/kg. The 1,500-mg/kg rat exhibited pain, weakness, and unconsciousness prior to death. Necropsy revealed slight congestion of the lungs and gastritis.

L

p-Toluidine: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥1,000 mg/kg. The 1,000-mg/kg rat exhibited pain, weakness, and cyanosis prior to death. Necropsy revealed damage to the liver and kidneys.

L

p-Nitroaniline: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥3,375 mg/kg. Lethal and sublethal doses caused weakness and cyanosis. Lethal doses also caused tremors. Necropsy revealed damage to the liver, and the kidneys were distended with albuminous fluid.

L

p-Nitrochlorobenzene: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥670 mg/kg. Lethal and sublethal doses caused cyanosis. Necropsy revealed liver necrosis and hemorrhage and incipient necrosis of the renal convoluted tubules.

L

p-Nitrophenetole: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥7,500 mg/kg. The 5,000-mg/kg rat exhibited pain, weakness, and bronchial irritation. The 7,500-mg/kg rat immediately became ill, unconscious, and died within 24 hours. Necropsy revealed congestion and edema in the lungs.

L

Alpha naphthol: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) were lethal at ≥1,000 mg/kg. Lethal doses caused diarrhea prior to death. Necropsy revealed congestion and edema in the lungs, albumin in the kidney tubules, and superficial necrosis of the stomach.

L

Naphthionic acid: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) at levels up to 7,500 mg/kg were not lethal. There were no gross or microscopic pathological effects.

M

Piperidine: Acute oral toxicity in rats is of moderate concern. Single oral gavage doses to rats (1/dose) were lethal at ≥450 mg/kg. Clinical signs included weakness and lethargy. Necropsy revealed edema of the lungs and necrosis of the stomach.

L

Diagen A: Acute oral toxicity in rats is of low concern. Single oral gavage doses to rats (1/dose) at levels up to 7,500 mg/kg were not lethal. Necropsy revealed evidence of chronic gastritis localized at the junction of the squamous and glandular portions of the stomach in the 7,500-mg/kg rat.